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Asthma exacerbations among asthmatic children receiving live attenuated versus inactivated influenza vaccines

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ABSTRACT

Objective: To investigate whether there is a difference in the risk of asthma exacerbations between children with pre-existing asthma who receive live attenuated influenza vaccine (LAIV) compared with inactivated influenza vaccine (IIV).

Material and methods: We identified IIV and LAIV immunizations occurring between July 1, 2007 and March 31, 2014 among Kaiser Permanente Northern California members aged 2 to <18 years with a history of asthma, and subsequent asthma exacerbations seen in the inpatient or Emergency Department (ED) setting. We calculated the ratio of the odds (OR) of an exacerbation being in the risk interval (1–14 days) versus the comparison interval (29–42 days) following immunization, separately for LAIV and IIV, and then examined whether the OR differed between children receiving LAIV and those receiving IIV ("difference-in-differences").

Results: Among 387,633 immunizations, 85% were IIV and 15% were LAIV. Children getting LAIV vs. IIV were less likely to have "current or recent, persistent" asthma (25% vs. 47%), and more likely to have "remote history" of asthma (47% vs. 25%). Among IIV-vaccinated asthmatic children, the OR of an inpatient/ED asthma exacerbation was 0.97 (95% CI: 0.82–1.15). Among LAIV-vaccinated asthmatic children the OR was 0.38 (95% CI: 0.17–0.90). In the difference-in-differences analysis, the odds of asthma exacerbation following LAIV were less than IIV (Ratio of ORs: 0.40, CI: 0.17–0.95, p value: 0.04).

Conclusion: Among children ≥2 years old with asthma, we found no increased risk of asthma exacerbation following LAIV or IIV, and a decreased risk following LAIV compared to IIV.

1. Introduction

In 2003, a nasally-administered, live attenuated influenza vaccine (LAIV, FluMist; MedImmune, Gaithersburg, MD) was approved by the US Food and Drug Administration for persons 2 years through 49 years of age [1,2]. From the 2007–2008 influenza season through the 2015–2016 season, the Advisory Committee on Immunization Practices (ACIP) recommended the use of either LAIV or inactivated influenza vaccine (IIV) in healthy children and adolescents ≥2 years of age [3–7], but either recommended, or cautioned, against use of LAIV in children with asthma, depending on the age of the child [4,6,7].

Concerns about use of LAIV in asthmatic children were partly based on a pre-licensure randomized placebo-controlled safety trial that suggested increased wheezing following LAIV [8]. However, asthma was not one of that trial's pre-specified endpoints, and this finding occurred in the context of >1500 statistical comparisons [8]. Subsequent evidence for increased asthma exacerbations among children older than 2 years of age receiving LAIV is limited. Another randomized trial comparing LAIV with IIV found non-significantly higher rates of hospitalization following LAIV among children 24–47 months old with a history of wheezing illness [9]. An open-label, non-randomized trial [10] found no increase in healthcare utilization attributed to respiratory illnesses in LAIV recipients, and two post-licensure studies (which excluded

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CI, Confidence Interval; ED, Emergency Department; HEDIS, Health Plan Employer Data and Information Set; ICD9, International Classification of Disease, 9th Revision, Clinical Modification; IIV, inactivated influenza vaccine; KPNC, Kaiser Permanente of Northern California; LAIV, live, attenuated influenza vaccine; OR, odds ratio; URI, upper respiratory infection.

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LAIV-vaccinated children with asthma) also found no increase in respiratory events following LAIV [11,12].

Few studies have examined adverse outcomes following LAIV in children with asthma or related respiratory conditions. An open-label field trial among children with intermittent wheezing, found no increase in acute asthma exacerbations in the first two weeks after LAIV vaccination [13]. Two randomized trials, one among children with asthma [14] and one among children with history of recurrent respiratory tract infections [15], and two post-marketing evaluations among children with asthma or recurrent wheezing [16,17], found no increase in adverse events among children receiving LAIV compared with IIV. A Cochrane review concluded there was no difference in asthma exacerbations between vaccine types in children over 2 years of age, while acknowledging the number of patients on which that conclusion was based was small [18].

In 2016, the ACIP made an interim recommendation that health care providers in the U.S. not use LAIV in the upcoming influenza season, citing poor effectiveness [19]. Nevertheless, some providers may elect to use LAIV [19], it continues to be recommended outside the U.S. [20,21], and may again be recommended for use in the U.S. in future seasons. Therefore, the safety of LAIV use in children with asthma remains a concern.

The goal of this study was to investigate the safety of LAIV administered to children and adolescents with a history of asthma and to evaluate whether its safety profile varied according to asthma severity. We compared LAIV versus IIV with respect to asthma exacerbations and other adverse outcomes in children and adolescents with a history of asthma within Kaiser Permanente Northern California (KPNC).

2. Materials and methods

2.1. Setting

KPNC is a nonprofit, integrated health care delivery system that provides comprehensive health services to 3.5 million members. KPNC databases capture immunizations and inpatient, emergency department (ED), and outpatient diagnoses. Immunizations are provided at no additional cost to members and are almost all received within the system. This study was approved by the Kaiser Permanente Northern California Institutional Review Board.

2.2. Study population

We identified all IIV and LAIV immunizations between July 1, 2007 and March 31, 2014 for KPNC members aged 2 through 17 years who were continuous KPNC members for two years prior to immunization (2009 Pandemic monovalent vaccines were not included). We retained immunizations for children with a history of asthma – those who received at least one International Classification of Diseases, 9th Revision, Clinical Modification (ICD9) diagnosis code for asthma (493.xx) any time prior to IIV/LAIV immunization. We included the same child over multiple seasons if they received immunizations in more than one season, and included children who received different vaccine types (IIV or LAIV) in successive seasons.

2.3. Classification by asthma severity

Children were classified into one of three groups at immunization: (1) "current or recent, persistent asthma"; (2) "current or recent, not persistent asthma"; (3) "remote history of asthma only". Children had "current or recent, persistent asthma" if they met at least one of these criteria in the year prior to immunization: (1) Asthma principal diagnosis from an inpatient hospitalization or ED visit; (2) $\geq$3 outpatient visits accompanied by an asthma diagnosis; (3) $\geq$1 prescriptions for an anti-inflammatory medication (i.e., inhaled corticosteroids, oral steroids, methylxanthines, mast cell stabilizers, leukotriene modifiers, and immunomodulators). Children had "current or recent, not persistent asthma" if they met at least one of these criteria during the two years prior to immunization: (1) Asthma principal diagnosis from an inpatient hospitalization or ED visit; (2) $\geq$1 outpatient visits accompanied by an asthma diagnosis; (3) $\geq$1 prescriptions for any asthma medication (anti-inflammatory or beta2 agonist); (4) Did not meet criteria for "current or recent, persistent asthma". Children not meeting the criteria above at the time of immunization had "remote history of asthma only". A child's asthma severity could change from one season to the next. We adapted the first two criteria from Wakefield and Cloutier [22] as proxies for asthma severity. Our criteria "current or recent, not persistent asthma" differs from the Wakefield and Cloutier criteria by looking back two-years rather than one, which allowed greater differentiation between it and "current or recent, persistent asthma".

2.4. Adverse outcomes

The primary outcome was acute asthma exacerbation, defined as: (1) acute inpatient hospitalization or ED visit accompanied by a principal diagnosis of asthma; or (2) a chart-confirmed outpatient asthma visit. We also identified all non-asthma outpatient visits as a "negative control", since we did not expect such visits to vary between IIV and LAIV recipients. Secondary analyses assessed non-asthma adverse outcomes: afebrile seizure, Bell's palsy, epistaxis, febrile seizure, fever, gastrointestinal disorders, migraine, otitis media, and sinusitis (Supplemental Table 1).

2.5. Medical record review: Validating outpatient asthma events

We reviewed charts for outpatient asthma visits to validate that the visits were for acute asthma exacerbations rather than routine asthma management or follow-up. We reviewed the medical records for all outpatient asthma visits during risk and comparison intervals following LAIV. These intervals were selected based on the literature or expert opinion. To compare risk for asthma exacerbation following LAIV versus IIV specifically among children with "remote history of asthma only" (who may have the lowest risk of asthma events), we also chart reviewed all post-IIV outpatient asthma visits for those children. Resource limitations precluded reviewing visits for IIV-vaccinated children with "current or recent, persistent" and "current or recent, not persistent" asthma.

2.6. Analyses

We used a case-centered, risk-interval, approach to evaluate the association between immunization and each outcome. The risk-interval aspect of our approach, which compares the odds of an event occurring in the risk interval versus the comparison interval, allows us to include only vaccinated individuals, thus reducing biases that might be introduced by including unvaccinated persons (who might differ from vaccinated persons in unmeasured ways) [27]. The case-centered aspect of our approach is similar to a stratified Cox proportional hazards model, but is much less computationally burdensome [23]. Like a Cox model, the case-centered approach can rigorously adjust for calendar time and reduce biases relating to temporal trends or seasonality. This approach has been described in detail [23] and been used in prior vaccine effectiveness and safety studies [24–27]. For each combination of vaccine (LAIV or IIV) and outcome (e.g., IP and ED asthma exacerbations), a logistic regression model was fit to a dataset consisting of one